VII CONGRESSO NAZIONALE B&M 2018

III SESSIONE

Dott. Roberto Cilia
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BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

VII CONGRESSO NAZIONALE B&M 2018

MICROBIOTA e PARKINSON

ROBERTO CILIA

CENTRO PARKINSON
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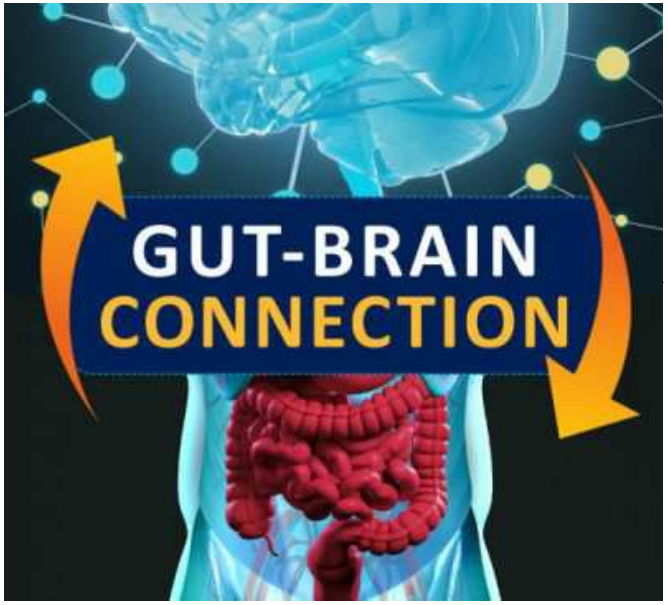
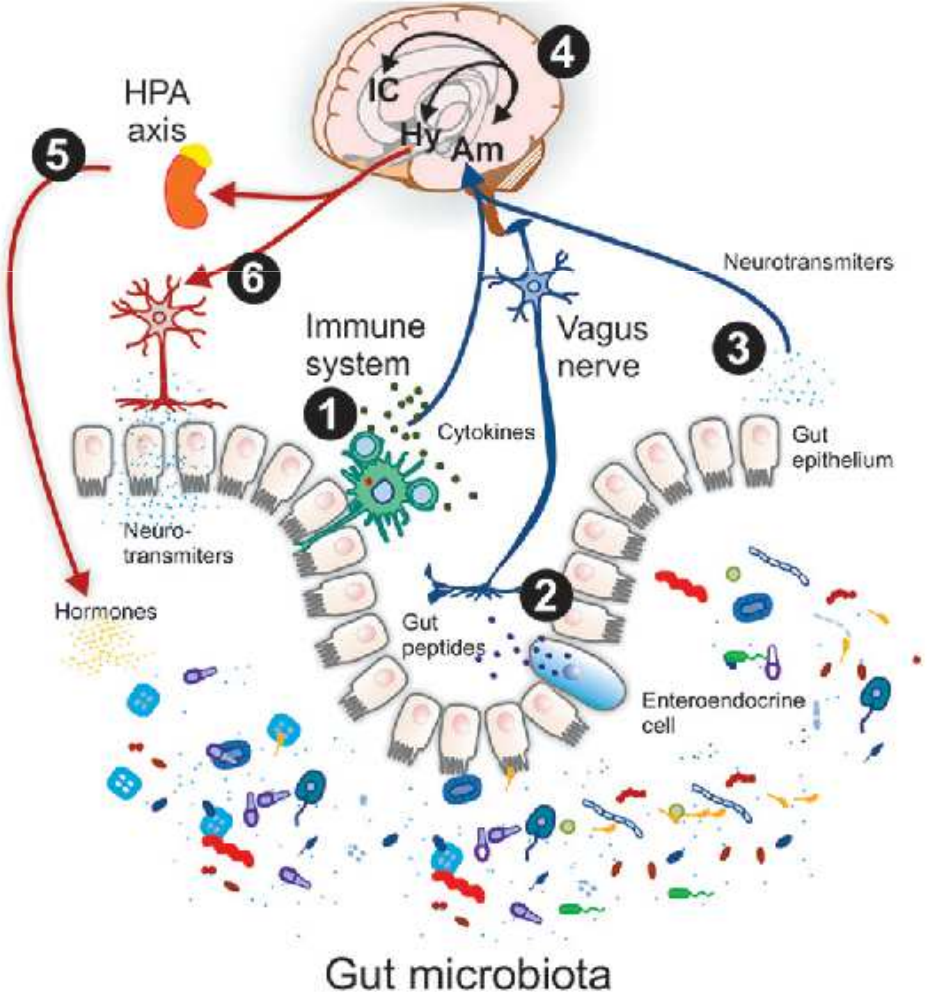
BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

Asse Intestino-Cervello

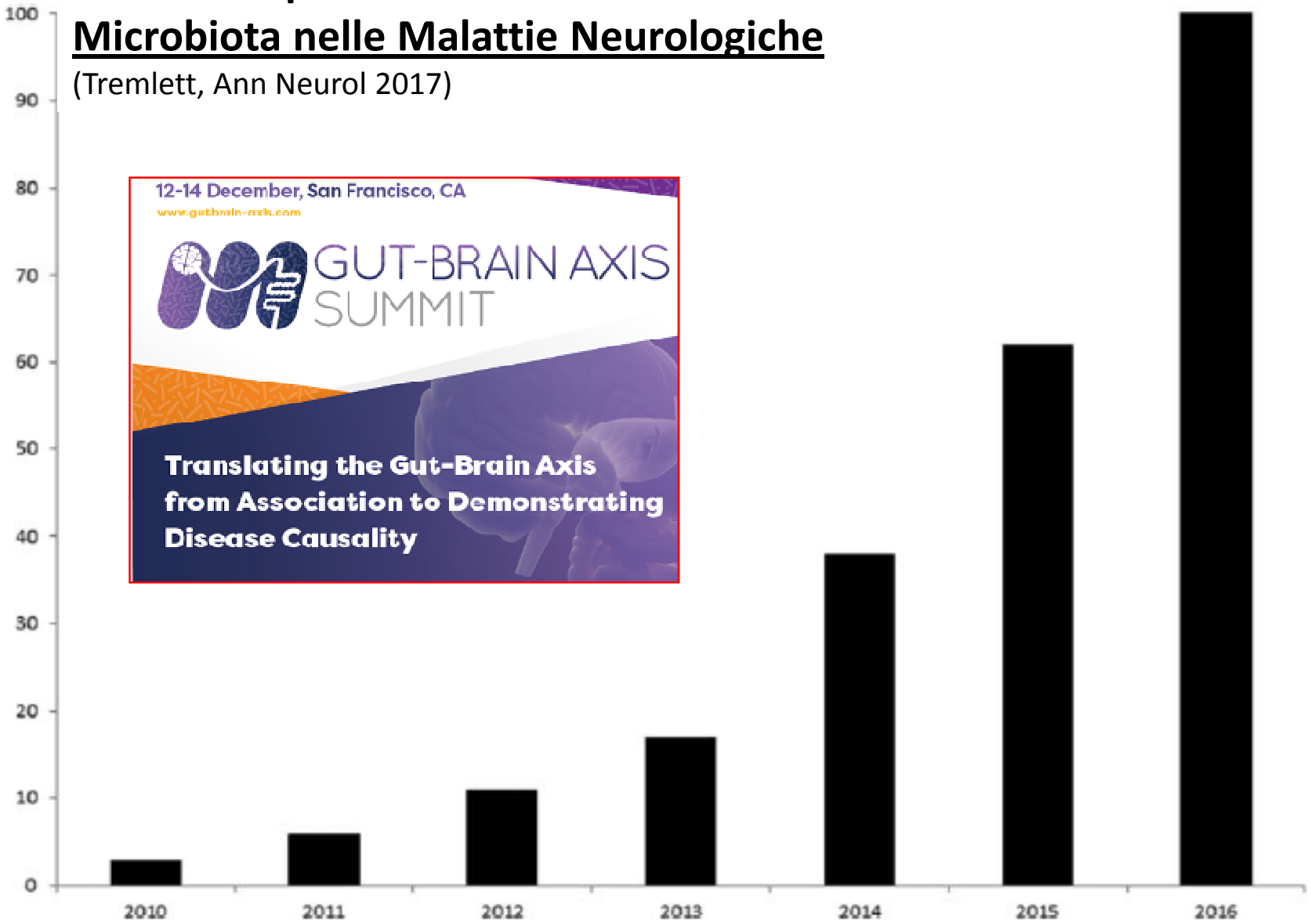
Molteplici vie di interazione: casualità o causalità?





Numero di pubblicazioni Scientifiche sul ruolo del <u>Microbiota nelle Malattie Neurologiche</u>

(Tremlett, Ann Neurol 2017)



Cos’è il MICROBIOTA?

Definizioni:

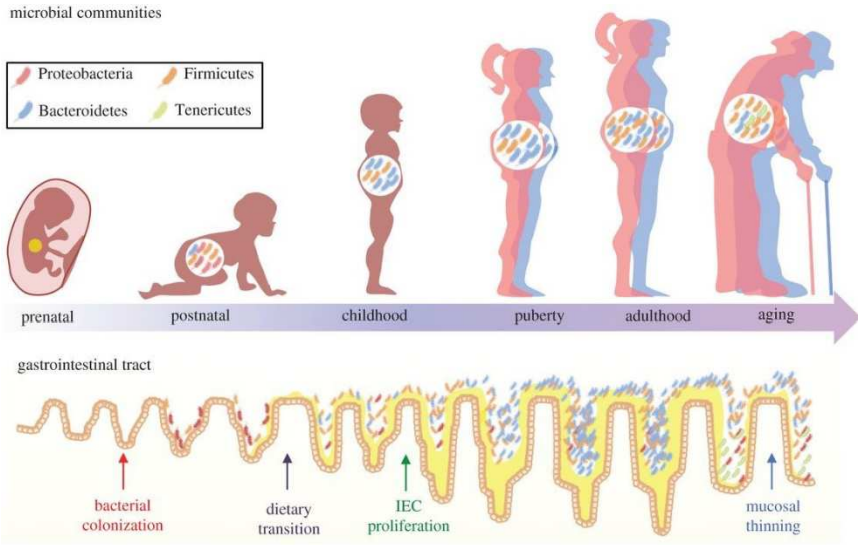
MICROBIOTA: insieme dei batteri che colonizzano l’organismo
MICROBIOMA: il genoma (DNA) dei batteri

Qual è la sua COMPOSIZIONE?

100.000 miliardi batteri
Composizione alla nascita (intestino fetale sterile)
Si modifica nel corso della vita.

Prima colonizzazione influenzata da

- Tipo di Parto (vaginale *vs.* cesareo)
- Allattamento (al seno *vs.* artificiale)

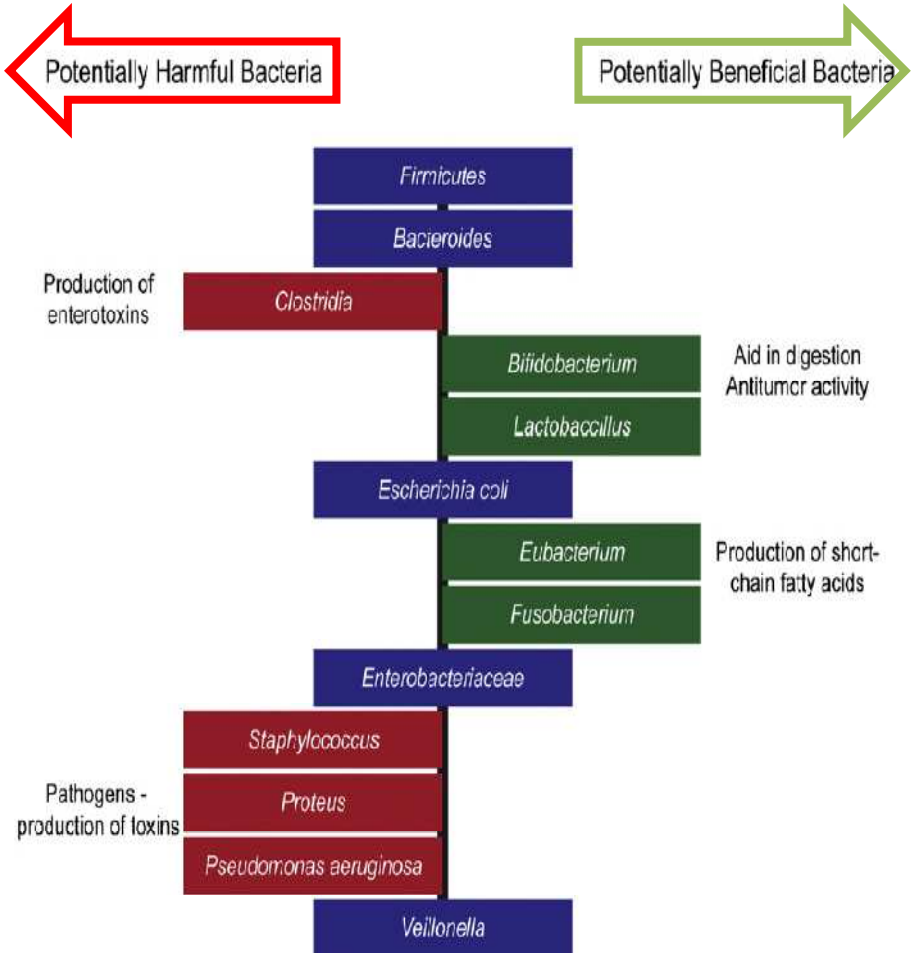


Qual è il suo RUOLO?

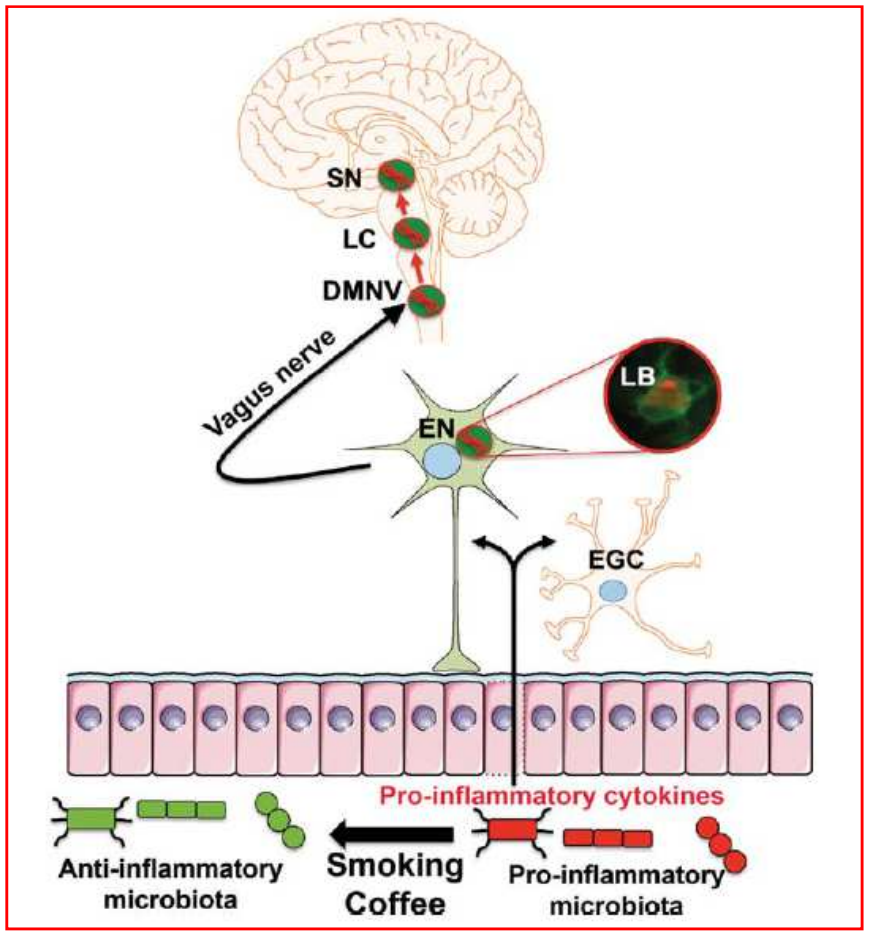
- Modulazione del sistema immunitario (ed es. citochine)
- Regola il metabolismo degli xenobiotici e la produzione di energia
- Sorgente di Vitamine (ad es. vitamina K)
- Influenza lo sviluppo del sistema nervoso enterico (5HT, GABA)

Ghaisas et al., Pharmacology & Therapeutics 2016

Proprietà Protettive (anti-infiammatorie) *vs.* Nocive (pro-infiammatorie) del Microbiota e Modulatori

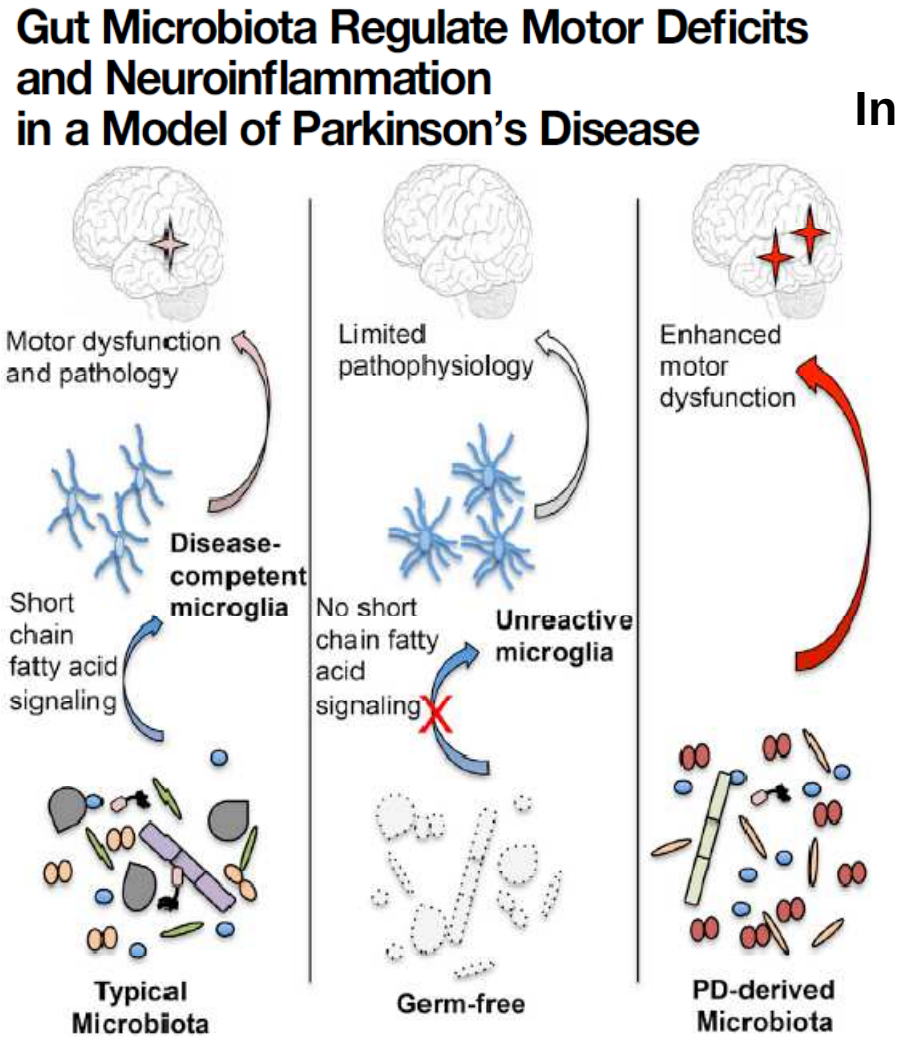


Una possibile spiegazione al ridotto rischio di PD nei fumatori ed all'assunzione di caffè?



Wu et al., Science 2011; Goldman et al., Mov Disord 2014;
Visanji, Mov Disord 2014; Ghaisas et al., Pharmacology & Therapeutics 2016

Ruolo del Microbiota nella progressione della patologia: ruolo dell'infiammazione *in vivo*



In α-syn overexpressing mouse model of PD:

- **Typical Microbiota** promote α-synuclein mediated brain pathology (via microglia activation by SCFAs signaling)
- Similar data from oral feeding by SCFAs without microbiota colonization
  -> What is the role of SCFAs?

- Depletion of gut bacteria (**Germ-Free**) reduces microglia activation, α-syn pathology and motor dysfunction

- **Human gut microbiota from PD cases** (but not from healthy controls) induce enhanced motor dysfunction

Sampson et al, Cell 2016

Microbiota e Rischio di Parkinson:

associazione casuale oppure causale?

Vagotomy and Subsequent Risk of Parkinson's Disease

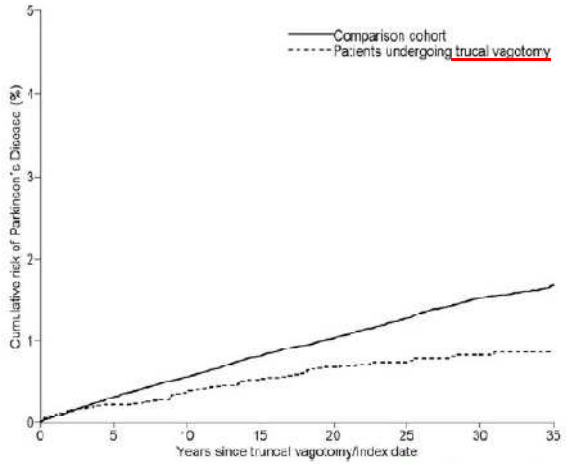
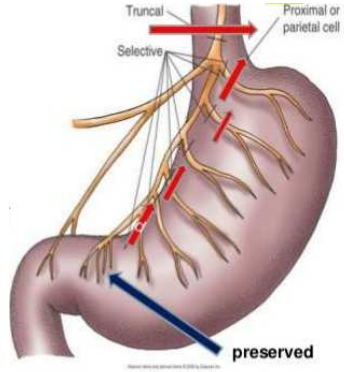


FIGURE 1: Cumulative incidence curves of Parkinson's disease for patients who underwent truncal vagotomy compared to a matched general population cohort.



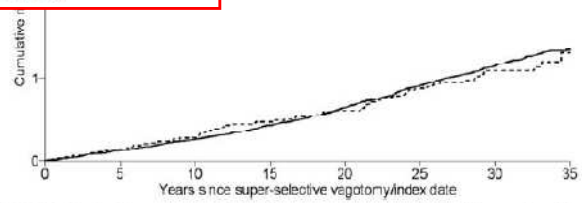
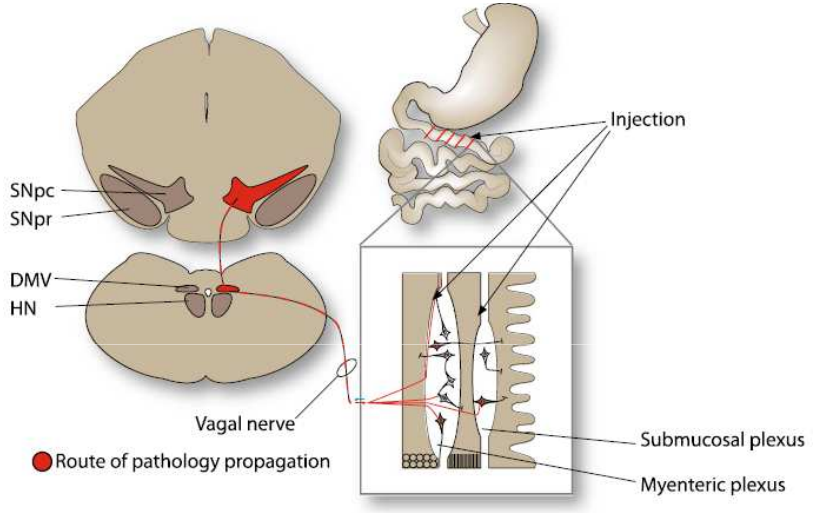


FIGURE 2: Cumulative incidence curves of Parkinson's disease for patients undergoing superselective vagotomy compared to a matched general population cohort.

Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats



Iniezione di lisato di cervello umano di paziente con Parkinson nella parete intestinale di animale:
Solo **α-sinucleina** (non albumina) è trasportata per via retrograda attraverso il nervo vago fino al cervello (in 6 gg).

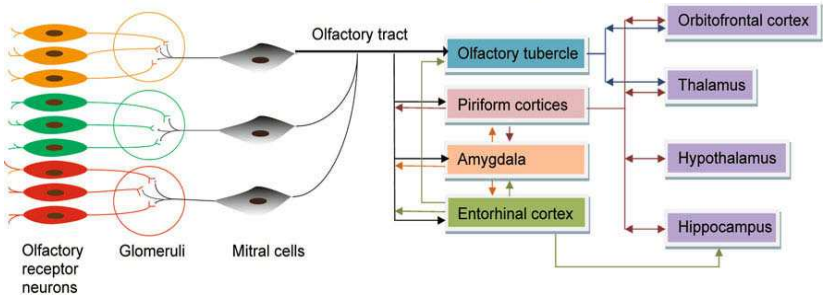
Svensson, Ann Neurol 2015
Derkinderen, Mov Disord 2014
Holmqvist, Acta Neuropathol 2014

Nasal/Oral & Gut Microbiota & Neurodegeneration:
Common triggers of protein misfolding?

Hyposmia: a possible biomarker of Parkinson's disease

Qian Xiao[1], Sheng Chen[1], Weidong Le[1,2]

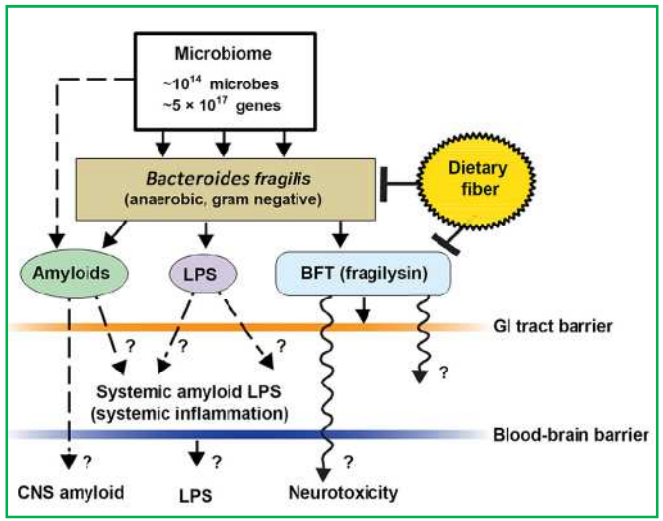
Neurosci Bull February 1, 2014, 30(1): 134–140.



Journal of Alzheimer's Disease 51 (2016) 979–984
DOI 10.3233/JAD-160152
IOS Press

Editorial

Microbes and Alzheimer's Disease



The Nasal and Gut Microbiome in Parkinson's Disease and Idiopathic Rapid Eye Movement Sleep Behavior Disorder

Anna Heintz-Buschart, PhD,[1] Urvashi Pandey, MS,[1] Tamara Wicke,[2,3] Friederike Sixel-Döring, MD,[2,3] Annette Janzen, MD,[3] Elisabeth Sittig-Wiegand, SN,[3] Claudia Trenkwalder, MD,[2,4] Wolfgang H. Oertel, MD,[3] Brit Mollenhauer, MD,[2,5]* and Paul Wilmes PhD[1]*

Movement Disorders, Vol. 00, No. 00, 2017

Oral and nasal microbiota in Parkinson's disease

Pedro A.B. Pereira, MSc [a, 1], Velma T.E. Aho, MSc, BA [a, 1], Lars Paulin, MSc [a], Eero Pekkonen, MD, PhD [b], Petri Auvinen, PhD [a], Filip Scheperjans, MD, PhD [b, *]

Parkinsonism and Related Disorders xxx (2017) 1–7

Oral dysbiosis increases the risk of Dementia!

Periodontopathy associated with **higher brain amyloid** in elderly

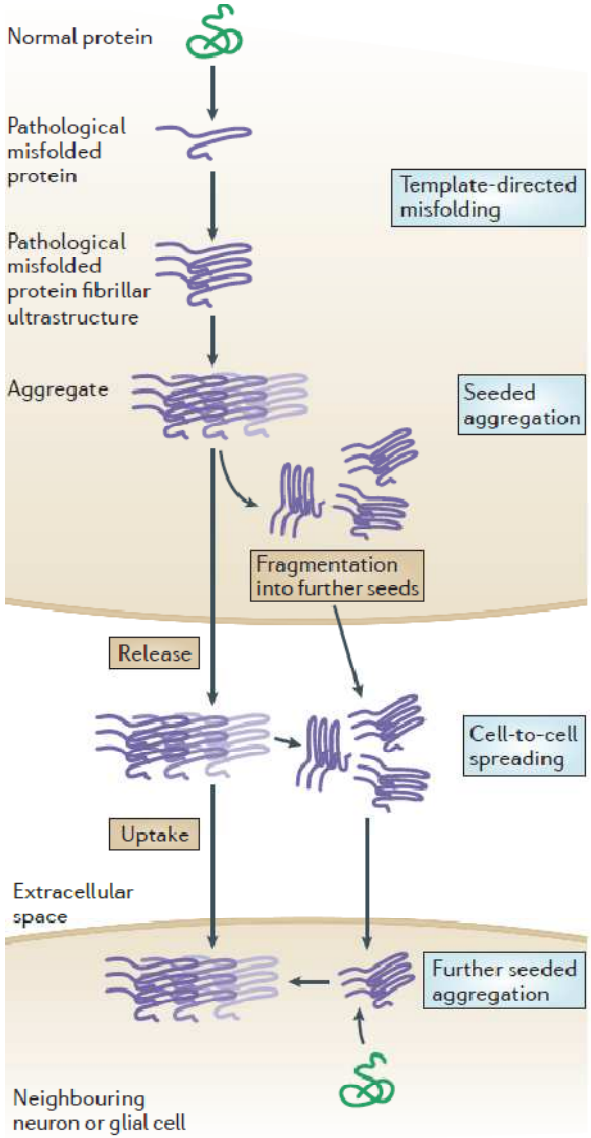
↑ risk: Irregular tooth brushing (prospective study in US, N=4,883)

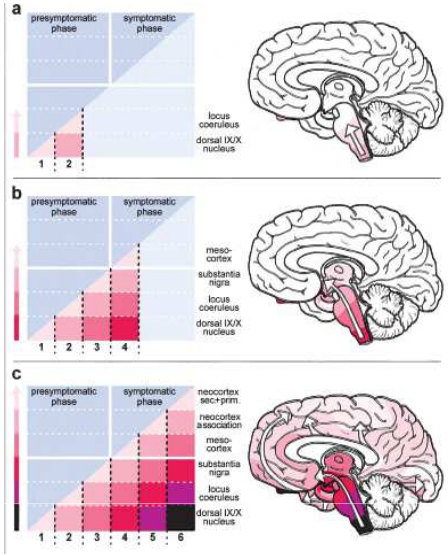
↑ risk: Tooth loss (Twin study is Sweden; Longitudinal US cohort)

Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly

Kamer et al., Neurobiol Aging 2015
Tamler et al., Ann Neurol 2017
Cattaneo et al, Neurobiol Aging 2017

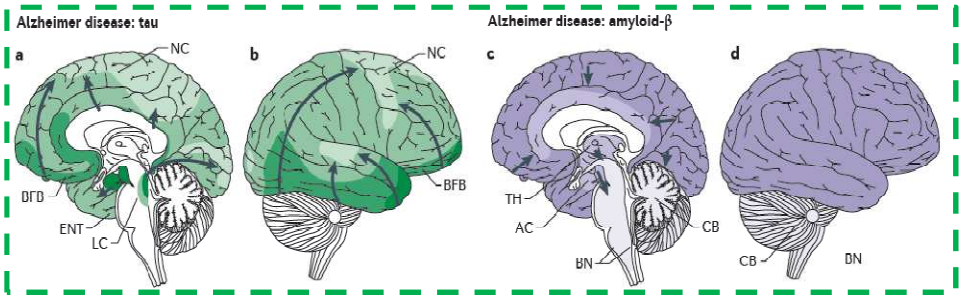
Cell-to-Cell Propagation of pathology in Neurodegenerative disorders

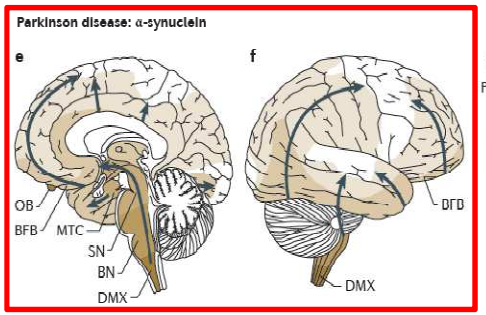


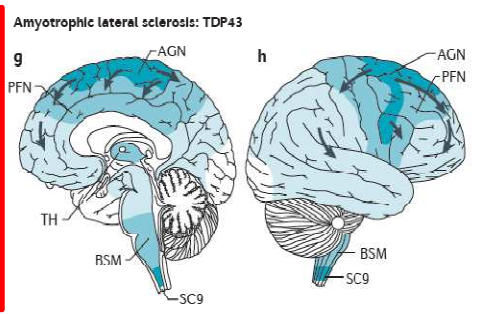


Evidences for a cell-to-cell (prion-like) propagation of pathology boosted research on the Braak hypothesis.

Similar mechanisms increasingly recognized in other degenerative disorders (eg AD, ALS)







Braak et al., 2003
Goedert, Science 2015
Brettschneider, Nat Rev Neurosci 2015

Is PD a Prion-like Disorder?

Prying into the Prion Hypothesis for Parkinson's Disease — YES

Patrik Brundin[1] and Ronald Melki[2]

The Journal of Neuroscience, October 11, 2017 · 37(41):9808–9818

NO — Parkinson's Disease Is Not Simply a Prion Disorder

D. James Surmeier,[1] José A. Obeso,[2,3] and Glenda M. Halliday[4,5]

The Journal of Neuroscience, October 11, 2017 · 37(41):9799–9807

Disagreement:

«STOCHASTIC SEEDING»

NO: 'Spreading follows rules, still undefined. Synaptic connectivity may be necessary'.

YES 'Seeding may happen in the brain (or gut/olfactory bulb), independently of cell-to-cell contacts'.

«UNCERTAIN RELATIONSHIP between LB PATHOLOGY, NEURONAL LOSS and CLINICAL MANIFESTATIONS»

a) PD without LB: how do we explain genetic forms without any LB (eg, Parkin)?

b) LB without cell loss: in regions with LB, decades may pass without any discernible cell loss

Agreement:

«SELECTIVE SUSCEPTIBILITY»

Yes, there is spreading of α-syn pathology. However, it is limited to a subset of neurons whose phenotype renders them susceptible to spreading.

Hypothesis:

- *Differences in the lysosomal autophagy? (e.g. GBA genotype)*
- *Receptors uptaking aggregation-prone species of α-syn?*

Microbiota in PKS: the (conflicting) results so far

	Scheperjans 2015	Keshavarzian 2015	Hasegawa 2015	Hill-Burns 2017	Unger 2016	Hopfner 2017	Heintz-Buschart 2017	Engen 2017
Study area	Finland	USA	Japan	USA	Germany	Germany	Luxemburg/ Germany	USA
Diagnosis	PD	PD	PD	PD	PD	PD	PD	MSA
N° of Cases/CNTR	72/72	38/36	52/36	197/130	34/34	29/29	76/78 (21 iRBD)	6/11
Samples	Fecal	Fecal and Mucosal	Fecal	Fecal	Fecal	Fecal	Fecal & Nasal	Fecal and Mucosal
Antibiotics-free / Nutrition Diaries	>1month / No	>3months / No	Not reported / No	Not reported / Nc (diet assessed)	Not reported / Nc	Not reported / No	Not reported / No	Not reported / No
Main Outcome	↓ Prevotellaceae PD phenotype -> Enterobacteriaceae	Anti-inflamm in HC Pro-inflamm in PD ↓ SCFAs ↑ LPS synthesis	↓ hydrogen-producing bacteria in PD ↑ LPS (↓ serum LPS-binding protein)	Diet fruits/vegetables ↑Xenobiotics degradation ↓ SCFAs PD duration-> Ruminococcaceae	↓ SCFAs	↑ Lactobacillaceae	80% microbiota differences PD vs HC similar in iRBD	Intestinal barrier dysfunction ↑ LPS synthesis
Decreased (fecal)	Prevotellaceae	Firmicutes, Lachnospiraceae, Coprobacillaceae, Roseburia (No Prevotellaceae)	Clostridium c/Clostridium I Bacteroides f.	Lachnospiraceae (No Prevotellaceae)	Firmicutes Lactobacillaceae (No Prevotellaceae) Bacteroidetes	None	None	Firmicutes
Increased (fecal)	Lactobacillaceae, Verrucomicrobiaceae, Clostridiales i.s. IV, Ruminococcaceae	Bacteroidetes, Proteobacteria Verrucomicrobia, Clostridiaceae,	Lactobacillaceae	Lactobacillaceae, Verrucomicrobiaceae Bifidobacteriaceae Christensenellaceae	Verrucomicrobia, Enterobacteriaceae	Lactobacillaceae Bifidobacterium Barnesiellaceae Enterococcaceae	Verrucomicrobia,	Bacteroidetes Proteobacteria
Clinical Features	UPDRS III Non-tremor phenotype iCOMT -> Lactob., Enterob	*Disease Duration* Treated ≠ Untreated	*Disease Duration* (No association between microbiota & medications)	iCOMT Anticholinergics Levodopa/Carbidopa	Not reported	No effect of iCOMT	Correlated with NMS (Bacteroides)	Not reported

Consistency: ↑ Verrucomicrobiacea (5/8); ↑ Lactobacillaceae (4/8); ↓ Firmicutes (3/8) & ↓ Lachnospiraceae (2/8)
Conflicting: Bacteroidetes; Clostridiaceae; Prevotella (only in 1/8)

More Questions than Answers?

1) Conflicting results due to methodological difficulties/issues

Question: *Shall we focus on biopsies (more stable flora) rather than fecal samples?*

2) Microbiota may be modifyied by PD medications and progression

Q*uestion:* *Are microbiota abnormalities a cause (or a consequence) of PD?*

Question: *What about De Novo PD (drug-naive)?*

3) Microbiota may promote α-syn aggregation and trigger cell-to-cell propagation

Question: *What about Tauopathies (PSP) vs. Synucleinopathies (PD-MSA)?*

4) Microbiota is influenced by several confounders

Question: *adjusting the analyses by nutrient intake, type of delivery and feeding?*

5) Beyond the gut, Beyond bacteria

Question: *What about nasal/oral microbiota (olfactory bulb as site of seeding)*

Question: *What about virome?*

Nostro Studio (1) Differenze tra Pazienti e Sani

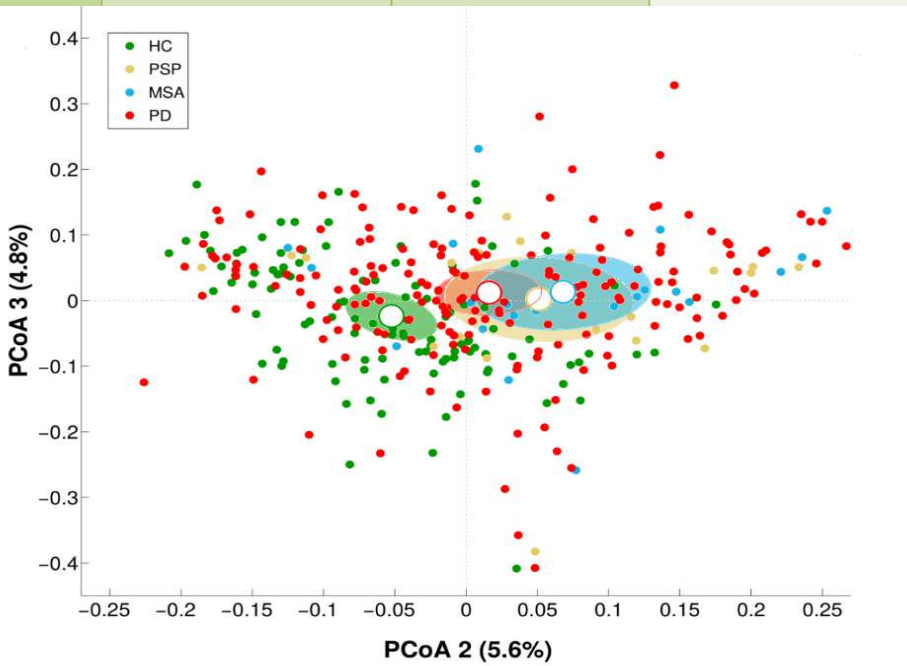
Healthy controls (N=113)	PD patients					MSA patients (N=22)	PSP patients (N=22)
	All cases (N=193)	De-novo (N=39)	Early-stage (N=57)[a]*	Mid-stage (N=53) [a]§	Advanced-stage (N=44) [a]#		

	DeNovo	PD
HC	Lachnospiraceae *	~~Ruminococcaceae~~ ** · Lachnospiraceae *** · Verrucomicrobiaceae *** · ~~Enterobacteriaceae~~ *** · ~~Porphyromonadaceae~~ ** · ~~Bifidobacteriaceae~~ ** · Christensenellaceae *** · ~~Coriobacteriaceae~~ * ·
DeNovo	--	~~Verrucomicrobiaceae~~ *

	PSP	MSA	PD
HC	Lachnospiraceae * · Verrucomicrobiaceae ** · ~~Enterobacteriaceae~~ * · Christensenellaceae ***	Verrucomicrobiaceae ** · ~~Bifidobacteriaceae~~ * · Christensenellaceae * · ~~Streptococcaceae~~ * · ~~Coriobacteriaceae~~ * ·	~~Ruminococcaceae~~ ** · Lachnospiraceae *** · Verrucomicrobiaceae *** · ~~Enterobacteriaceae~~ *** · ~~Porphyromonadaceae~~ ** · ~~Bifidobacteriaceae~~ ** · Christensenellaceae **
PSP	--	~~Bifidobacteriaceae~~ * · ~~Streptococcaceae~~ ** ·	~~Prevotellaceae~~ * · Christensenellaceae ** · ~~Streptococcaceae~~ * ·
MSA		--	~~Streptococcaceae~~ * ·

Analisi statistiche corrette per i seguenti Fattori ('confounders')

- Età, sesso, allattamento, BMI, stipsi
- Abitudini Alimentari (intake calorico, proteine, fibre, alcol, acqua)
- Terapia Farmacologica (use of COMT-i)



Nostro Studio (2a) Microbiota è modulato dalla progressione della Malattia di Parkinson?

Taxonomic Level [b]			Healthy controls (N=113)	De-novo PD (N=39)	Early PD (N=57)[a]*	Mid-stage PD (N=53) [a]§	Advanced PD (N=44) [a]#	P-value for trend [e]
Phylum	***Family***	***Genus***	*Mean (SD) [c] abundance*	*Mean (SD) [c] Adj. diff. (SE) [d] [P-value]*	*Mean (SD) [c] Adj. diff. (SE) [d] [P-value]*	*Mean (SD) [c] Adj. diff. (SE) [d] [P-value]*	*Mean (SD) [c] Adj. diff. (SE) [d] [P-value]*	
	Lachnospiraceae		19.39 (12.98)	14.43 (8.71)* -6.32 (2.66) **[0.019]**	16.38 (11.42)** -4.29 (2.14) **[0.049]**	13.22 (8.94)** -5.29 (2.49) **[0.016]**	12.66 (8.61)** -5.20 (2.59) **[0.041]**	**0.044**
		Roseburia	5.20 (6.16)	2.85 (3.60) -2.50 (1.23) **[0.045]**	3.04 (5.70)*** -2.24 (1.11) **[0.039]**	1.79 (2.50)*** -3.02 (1.17) **[0.011]**	2.26 (3.98)*** -2.37 (1.18) **[0.048]**	0.907
		Unclassified	4.45 (3.80)	3.28 (2.76) -1.58 (0.79) **[0.047]**	3.42 (3.22)** -0.95 (0.67) [0.162]	2.85 (2.60)*** -1.89 (0.74) **[0.011]**	2.50 (2.56)** -1. 39 (0.79) **[0.015]**	0.600
	Lactobacillaceae		0.12 (0.40)	0.10 (0.36) -0.01 (0.08) [0.908]	0.90 (3.43) 0.47 (0.35) [0.189]	1.10 (2.58) 1.10 (0.33) **[<0.001]**	2.46 (4.75) 1.16 (0.52) **[0.028]**	**0.018**
		Lactobacillus	0.12 (0.39)	0.10 (0.36) -0.01 (0.08) [0.907]	0.87 (3.34) 0.47 (0.35) [0.179]	1.07 (2.49) 1.06 (0.31) **[<0.001]**	2.39 (4.68) 1.12 (0.51) **[0.032]**	**0.019**
Verrucomicrobia			1.62 (3.65)	2.67 (4.30) 1.09 (0.83) [0.194]	4.26 (6.46)*** 2.53 (0.85) **[0.004]**	4.47 (7.74)*** 2.91 (1.11) **[0.010]**	6.27 (9.75)** 5.30 (1.35) **[0.001]**	**0.049**
	Verrucomicrobiaceae		1.59 (3.64)	2.66 (4.29) 1.11 (0.83) [0.184]	4.19 (6.48)*** 2.52 (0.85) **[0.004]**	4.42 (7.69)*** 2.87 (1.12) **[0.011]**	6.23 (9.74)** 5.31 (1.35) **[<0.001]**	**0.047**
		Akkermansia	1.58 (3.63)	2.66 (4.28) 1.11 (0.83) [0.182]	4.17 (6.46)*** 2.52 (0.85) **[0.004]**	4.40 (7.67)*** 2.86 (1.11) **[0.011]**	6.20 (9.72)** 5.29 (1.35) **[<0.001]**	**0.048**

Nostro Studio (2b) Microbiota modula la progressione della Malattia di Parkinson?

a) Gravità dei Sintomi Motori (UPDRS-III)

-> Lactobacillaceae (Lactobacillus)

b) Sintomi Motori Non-Responsivi alla Levodopa

-> Lachnospiraceae, Lactobacillaceae, Verrucomicrobia

c) Disturbo del Cammino

-> Lachnospiraceae

d) Disturbi di Equilibrio

-> Lachnospiraceae, Lactobacillaceae

e) Deficit Cognitivi

-> Lactobacillaceae (Lactobacillus, Faecalibacterium)

<u>Razionale per Possibili Terapie Neuroprotettive?</u>

Modulazione del Microbiota (Probiotici? Trapianto fecale?)

ACKNOWLEDGEMENTS

Prof. Gianni Pezzoli, MD

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Dott. Michela Barichella, MD

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Dott. Valentina Ferri, MD

Nutrition Specialist

Parkinson Institute, Milan

Dott. Serena Caronni, PsyD

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Parkinson Institute, Milan

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Dr Gianluca De Bellis, PhD

Dr Clarissa Consolandi, PhD

Dr Marco Severgnini, PhD

Fondazione Grigioni per il Morbo di Parkinson (Milano, IT)

www. parkinson.it

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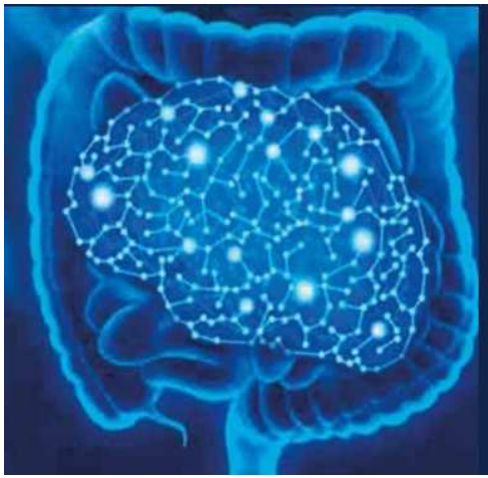

"All diseases begins in the gut"
Hippocrates 400 B.C.

Grazie

BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS